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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,806	03/12/2002	Ben-Quan Shen	P1735R1	4225

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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,806	SHEN ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 8, 10, 14, 15, 18, 19, and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18 and 19* is/are allowed.

6)☒ Claim(s) *1, 2, 8, 10, 14, 15, 18, 19, and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0404*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

Applicant's amendment filed April 30, 2004 is acknowledged. Claim 4 has been canceled. Claims 1 and 14 are amended. Claim 21 is new. Claims 1, 2, 8, 10, 14, 15, 18, 19, and 21 are pending and under consideration. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

The objection to the specification regarding the use of trademarks is withdrawn in response to Applicant's amendments to the specification.

The rejection of claims 1, 2, 8, 10, and 14 under 35 U.S.C. 102(b) as being anticipated by Martin *et al.* (International Publication WO 98/20027) is withdrawn in response to Applicant's amendments to the claims. The claims are now drawn to VEGF receptor agonists selective for the KDR receptor, and Martin *et al.* do not teach such a limitation.

The rejection of claims 1, 2, 4, 8, 10, 14, 15, and 18 under 35 U.S.C. 102(a) and 102(e) as being anticipated by Keyt *et al.* (U.S. Patent 6,020,473) is withdrawn in response to Applicant's amendments to claims 1, 2, 8, 10, 14, 15, and 18 and the cancellation of claim 4. Keyt *et al.* do not teach administration of VEGF variants for the treatment of NO-associated disorders or for the treatment of hypertension, diabetes, angina, thrombosis, heart failure or atherosclerosis.

The rejection of claims 1, 2, 4, 8, 10, 14, 15, 18, and 19 under 35 U.S.C. 103(a) as being unpatentable over Keyt *et al.* is withdrawn in response to the cancellation of claim 4 and in view of the fact that the Keyt *et al.* patent is assigned to the assignee of the present invention and that at the time the invention was made they were owned by the same person or subject to an obligation of assignment to the same person.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 recites the limitation "effective amount of VEGF" in the first line of the claim. The claim is dependent on claim 1, which as amended is now drawn to a method of administering a VEGF variant and not VEGF. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 8, and 10 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained for reasons of record on p. 3-4 of the office action of paper no. 1203. The rejection of claim 4 under 35 U.S.C. 112, first paragraph for lack of enablement is withdrawn in view of the cancellation of claim 4. Applicants argue that one of skill in the art reading the specification would be able to make and use the methods as claimed without undue experimentation. Applicants argue that because nitric oxide (NO) and endothelial NO synthase (eNOS) are involved in various VEGF-induced activities, and because VEGF treatment upregulates eNOS expression and activity, VEGF or VEGF receptor agonists would be useful in the treatment of NO-associated disorders (p. 8 of response). Applicants further argue that the multiple examples of NO-associated disorders that they disclose in the specification are representative of the genus of NO-associated disorders, and that one of skill in the art would predict that Applicants' claimed methods would also be applicable to other NO-associated disorders within the genus (p. 9 of response).

Applicants' arguments have been fully considered but have not been found to be persuasive. The claims are all drawn to methods of administering VEGF variants or VEGF

receptor agonists in order to treat a NO-associated disorder. As stated above, Applicants teach that VEGF treatment upregulates eNOS expression and activity. Thus, whenever VEGF variants or VEGF receptor agonists are administered they will be increasing expression of NO. However, there are some situations where increased levels of NO are harmful rather than beneficial. As stated in the previous office action, it is known that levels of nitric oxide are increased in hypotension, sepsis, stroke, myocardial depression, and inflammatory responses. In such situations, the NO-associated disorder would not be treated by administering a VEGF variant or agonist that would increase the level of NO.

One of skill in the art would first need to determine whether or not nitric oxide is associated with a disorder. Then one would need to determine whether nitric oxide levels are increased or decreased in the disorder. In addition, one would need to determine whether increasing nitric oxide levels would be effective in treating the disorder. Only then would one skilled in the art be able to practice the method as taught by Applicants. Because of the lack of working examples, the breadth of the claims, and the lack of direction provided by the Applicants, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

The rejection of claim 15 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained for reasons of record on p. 4-5 of the office action of paper no. 1203. Claims 1, 2, 8, 10, 14, and 21 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VEGF variants that selectively bind KDR receptors, wherein the variants have the amino acid substitution(s) D63S, G65M or G65A, and/or L66R or L66T, does not reasonably provide enablement for any VEGF variant or VEGF receptor agonist that selectively binds KDR receptors. Applicants argue that the specification provides representative examples of VEGF variants and VEGF receptor agonists such that the full scope of the claims is enabled. Applicants argue that they have provided working examples for a method of producing VEGF variants selective for the KDR receptor and that they have disclosed 29 different VEGF variants selective for the KDR receptor (p. 10 of response).

Applicants have provided examples of VEGF variants wherein substitutions are made in either the FLT-1 receptor binding region or the KDR receptor binding region of VEGF. Of the

29 different VEGF variants taught by Applicants in Table 2 of the specification (p. 36-37), the substitutions occur at residues 17, 18, 21, 22, 25, 63, 65, and/or 66. Applicants teach that these residues are important for binding to the FLT-1 receptor but not for binding to the KDR receptor (see p. 31, Example 6). Claims 1, 2, 8, 10, 14, 15, and 21 are generically drawn to methods of administering any VEGF variant that is selective for the KDR receptor. Applicants state that VEGF variants include substitutions, deletions, and insertions, so long as the VEGF has the desired activity (p. 13, lines 17-24). Such VEGF variants may have mutations anywhere within the VEGF sequence, yet one of skill in the art would not expect VEGF variants having substitutions not within the KDR receptor binding region or FLT-1 receptor binding region to be more selective or less selective for the KDR receptor. Applicants have not provided any guidance for which residues outside of the KDR receptor binding region or FLT-1 receptor binding region, when substituted, deleted, or mutated in any way would be selective for the KDR receptor. Similarly, VEGF receptor agonists are defined as agents that have affinity to and activate receptors normally activated by a naturally occurring ligand (see p. 10 of specification). The only VEGF receptor agonists selective for the KDR receptor taught by Applicants are the previously stated ones found in Table 2 of the specification. Applicants have not provided examples of any other VEGF receptor agonists that are selective for the KDR receptor. One of skill in the art would not know how to make and/or use such VEGF variants or VEGF receptor agonists. Although Applicants argue that they have taught working examples for how to screen for VEGF variants or VEGF receptor agonists selective for the KDR receptor, Applicants have only provided a starting point for experimentation.

Since detailed information regarding the structural requirements of the VEGF variants is lacking, the state of the prior art, the unpredictability of the art, the lack of working examples, the breadth of the claims, and the lack of direction provided by the Applicants, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Conclusion

Claims 18 and 19 are allowed.

Claims 1, 2, 8, 10, 14, 15, and 21 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RBK
6/18/04

JANET ANDRES
PATENT EXAMINER